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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,313	LOOSMORE ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 January 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/18/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-7 and 29, in the reply filed on 11/24/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8-28 were cancelled by Applicant. Claims 1-7 and 29 are pending and currently under examination.

Specification

2. The disclosure is objected to because of the following informalities: Pages 6, 17 and 33 refer to patent applications yet do not include the Serial Numbers, but instead have blank spaces. Applicants should either provide the Application Serial number or draw a line through the blank space. Otherwise, the application will be rejected by the Printer at the time of printing.

The 'Brief Description of the Drawings' has some minor informalities regarding Figure labels. For instance, 'Figure 11' should be changed to 'Figure 11A-11C'; 'Figure 14' should be changed to 'Figure 14A and 14B'; 'Figure 4' should be changed to 'Figure 4A and 4B' (see also drawing objection below); and Figure 8' should be changed to 'Figure 8A and 8B' (see also drawing objection below).

Appropriate correction is required.

Drawings

3. The drawings are objected to because they are not accurately labeled. For instance, there is a 'Figure 4' and a 'Figure 4B'; the 'Figure 4' should be labeled 'Figure 4A'. There is a 'Figure 8' and a 'Figure 8B'; the 'Figure 8' should be labeled 'Figure 8A'.. Additionally, the drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Panels labeled "A', 'B', etc. are recited in the 'Brief Description of the Drawings' yet these Panels are not labeled in the Figures.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Incorporation by Reference

4. The specification refers to several U.S. Patents and U.S. Patent applications which are to be incorporated by reference. Prior to allowance of an application that incorporates essential material by reference to a pending U.S. application, it shall be determined if the referenced application has been published or issued as a patent. If these U.S. Patent applications have been published as U.S. Patents, Applicant must amend the specification to include the appropriate U.S. Patent Serial No. in lieu of the application number.

If the referenced application has not been published or issued as a patent, applicant will be required to amend the disclosure of the referencing application to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating the amendatory material consists of the same material incorporated by reference in the referencing application.

If an application as filed incorporates essential material by reference to a U.S. patent or a pending and commonly owned U.S. application, applicant may be required prior to examination to furnish the Office with a copy of the referenced material together with an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the copy consists of the same material incorporated by reference in the referencing application. However, if a copy of a printed U.S. patent is furnished, no affidavit or declaration is required.

Claim Rejections - 35 USC § 112

5. Claims 1-7 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 do not recite that the composition comprises 'isolated and/or purified' proteins. Accordingly, the compositions read on a whole cell multi-component vaccines comprising a strain of *H.influenzae* and a whole cell strain of *M.catarrhalis*". Based on the teachings of the specification, this is not the subject matter which applicant(s) regard as their invention. The specification teaches the use of 'isolated' antigens and not whole-cell organisms comprising said antigens. However, while the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. The claims must be amended to reflect Applicant's invention, e.g., "isolated" antigens.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "a multi-valent immunogenic composition for conferring protection in a host against disease caused both by *H.influenzae* and *M.catarrhalis*, which comprises: (a) an isolated and purified analog of *H.influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of natural Hin47 protein, (b) an isolated and purified *H.influenzae* adhesin (Hia) protein of

a non-typeable strain of *H.influenzae*, c) an isolated and purified high molecular weight protein of a non-typeable strain of *H.influenzae*, and (d) and isolated and purified outer membrane protein of *M.catarrhalis* having an apparent molecular mass of about 200 kDa, as determined by SDS-PAGE" and 'method of immunizing a host against disease caused by infection with both *H.influenzae* and *M.catarrhalis*, including otis media, which comprises administering to the host an immunoeffective amount of said composition' , does not reasonably provide enablement for "A multi-valent immunogenic composition for conferring protection in a host against disease caused both by *H.influenzae* and *M.catarrhalis*, which comprises: at least four different antigens, comprising at least one antigen from *H.influenzae* and at least one antigen from *M.catarrhalis*, at least three of which antigens are adhesins and at least one of which adhesins is from *M.catarrhalis*", nor is it 'enabled for methods of immunizing a host against disease caused by infection with both *H.influenzae* and *M.catarrhalis*, including otis media, which comprises administering to the host an immunoeffective amount of said composition' or for a composition in which one of the three antigens is a *H.influenzae* surface fibril protein (hsf) . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4)

the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are broadly drawn to an immunogenic composition conferring protection in a host against disease caused both by *H.influenzae* and *M.catarrhalis*, which comprises: at least four different antigens, comprising at least one antigen from *H.influenzae* and at least one antigen from *M.catarrhalis*, at least three of which antigens are adhesins and at least one of which adhesins is from *M.catarrhalis*. The claims allow for these antigens to be *any* three adhesin antigens and the one antigen to be any *H.influenzae* or *M.catarrhalis* antigen. The scope of the claims requires that this multivalent composition confers protection against diseases caused by both *H.influenzae* and *M.catarrhalis.* The specification teaches that there are no vaccines known to protect against *M.catarrhalis*. See page 2, lines 15-16. The only *M.catarrhalis* antigen taught in the instant specification is the 200kDA adhesin protein. It is taught to be found in 73 out of 74 otitis-media derived *M.catarrhalis* strains. The specification is not enabled for any other antigen from a *M.catarrhalis* strain, much less another *M.catarrhalis* adhesin antigen. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful

conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." It would take undue experimentation for one of skill in the art to discover a *M.catarrhalis* antigen, other than the 200kDA adhesin protein, let alone one which would successfully work in a multi-valent vaccine and not compete with the other antigens in the composition. There is no guidance provided regarding how to find another suitable *M.catarrhalis* antigen, much less an adhesin antigen. The vaccine art is highly unpredictable, particularly with respect to multivalent vaccines. See Ward. Bulletin of the World Health Organization. 2000. 78(2): 205-215. Often times, the multi-valent vaccines produce a less potent immune response than a single antigen due to the competition among antigens in the multi-valent vaccine. It would be invention and not mere experimentation for one of skill in the art to discover another *M.catarrhalis* antigen which would work in a similar manner as the 200kDA adhesin protein which is taught. The prior art, at the time of filing, had not taught any adhesins from *M.catarrhalis* other than the 200kDa adhesin.

Additionally, the specification has only provided results and experiments for the multi-valent immunogenic composition for conferring protection in a host against disease caused both by *H.influenzae* and *M.catarrhalis*, which comprises: (a) an isolated and purified analog of *H.influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of natural Hin47 protein, (b) an isolated and

purified *H.influenzae* adhesin (Hia) protein of a non-typeable strain of *H.influenzae*, c) an isolated and purified high molecular weight protein of a non-typeable strain of *H.influenzae*, and (d) and isolated and purified outer membrane protein of *M.catarrhalis* having an apparent molecular mass of about 200 kDa, as determined by SDS-PAGE". The current claims allow for any four antigens. The only *H.influenzae* antigens taught in the instant specification are the HMW antigens, the Hia antigen, the isolated and purified analog of *H.influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of natural Hin47 protein, and the Hsf protein. However, the Hsf protein was not used in any of the experiments disclosed in the specification, nor was a non-proteolytic heat shock protein of *H.influenzae*. It is unclear that any other combination of antigens would have the same success in conferring protection in a host against disease, including otitis media, caused by *H.influenzae* and *M.catarrhalis*. The prior art has taught that it is extremely unpredictable to predict which antigens will have success in treating otitis media. The prior art teaches that *H.influenzae* bacterial proteins which produce effective bactericidal antibodies and effectively reduce bacteria in infant mice which have been passively immunized with said bactericidal antibodies do not always turn out to be effective as vaccines. For example, the prior art teaches that the *H.influenzae* P6 outer membrane protein which seemed like a very promising vaccine candidate due to its ability to produce effective bactericidal antibodies and use them to effectively reduce *H.influenzae* infection in infant rats did not prove to be an effective vaccine in children who are in need of a vaccine against *H.influenzae*. Murphy et al. (Pediatr. Infect. Dis. J., 1989. 8(1): S66-S68) disclose that antibodies to P6

immunopurified from pooled normal human serum are bactericidal for nontypeable *H.influenzae* and antibodies to P6 were shown to be protective in the infant rat model of meningitis (page S67, column 2, paragraph 1). Murphy et al. indicate that P6 had all the promising characteristics to indicate that it might be an effective vaccine to prevent infections caused by *H.influenzae* and stated that the next step in determining its effectiveness would be clinical vaccine trials. See page S68, paragraph 2. Yamanaka et al. (J.Pediatrics, 1993. 122(2): 212-218) demonstrate that the P6 antigen was not effective in children who have repeated episodes of otitis media, an infection caused by *H.influenzae*, as these children did not mount a normal response to P6 and failed to have a secondary immune response on repeated challenge (page 217, column 1, second paragraph). Murphy et al. (Pediatr. Infect. Dis. J., 1989. 8(1): S66-S68) discloses on page S66, col. 1, paragraph 2, that when considering a bacterial antigen as a vaccine there are three major considerations to be raised. See column 1, paragraph 2, page S66. The instant specification has not demonstrated that the antigens included in the scope of claim 1, meet the considerations listed as (2) and (3) by Murphy et al, i.e., these random antigens have not been shown to generate protective antibody such that antibody to the antigen prevents disease and it has not been demonstrated that it is a good immunogen such that protective antibodies are elicited in the population at risk and that these antibodies persist for sufficient time to provide protection throughout the risk period. Since the prior art as demonstrated by Murphy et al. and Yamanaka et al. teach that success of *H.influenzae* proteins in producing bactericidal antibodies which may effectively clear bacteria in the infant rat

model do not correlate to success as a vaccine in active immunizations in populations which would benefit from the *H.influenzae* vaccine the information provided in the instant specification is not deemed sufficient to enable claims to vaccines and methods of immunizing.

To find a successful combination of multiple antigens is even more unpredictable. One of the major concerns in the development of the multicomponent vaccine is that a tandem arrangement of the antigens and or epitopes in the multivalent vaccine construct might result in a protein that fails to elicit antigen or epitope-specific immune responses caused by antigen/epitope competition and/or problems related with antigen processing and presentation. See Shi et al. Pro.Natl.Acad.Sci., February 1999; 96(4): 1615-1620. The prior art teaches that as the number of antigens in a vaccine increases so does the vaccine-associated adverse effects. It is taught that many multi-valent, multi-organism vaccines will induce immune responses which are quantitatively and qualitatively different from those engendered by single antigen or single organism products. See Ward. Bulletin of the World Health Organization. 2000. 78(2): 205-215, page 209, column 2. Ward teaches that is now well established that simultaneous administration of antigens A + B can alter the magnitude and pattern of immune responses to both A and B. It is unclear whether or not these altered immune responses generated by these multi-valent vaccines are equally efficacious. *B.pertussis* multi-valent vaccines, for instance, have been shown to be considerably problematic, particularly at trivalent and higher valency. See Ward, page 209.

In view of the teachings of *In re Wands*, 8 USPQ2d 1400, it has been determined that the level of experimentation to produce the vaccines and use them in methods of immunizing are undue. It has been set forth above that 1) the experimentation required to generate a multi-valent vaccine which provides protective against diseases caused by both *H.influenzae* and *M.cattharlis* and immunizing a host immunizing a host against *H.influenzae* and *M.cattharlis* infection would be great as 2) there are no immunological experiments provided, with the exception of the "a multi-valent immunogenic composition for conferring protection in a host against disease caused both by *H.influenzae* and *M.catarrhalis*, which comprises: (a) an isolated and purified analog of *H.influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of natural Hin47 protein, (b) an isolated and purified *H.influenzae* adhesin (Hia) protein of a non-typeable strain of *H.influenzae*, c) an isolated and purified high molecular weight protein of a non-typeable strain of *H.influenzae*, and (d) and isolated and purified outer membrane protein of *M.catarrhalis* having an apparent molecular mass of about 200 kDa, as determined by SDS-PAGE", to demonstrate that the claimed immunogenic compositions are capable of mounting an efficient protective, immune response in an at risk population and, more importantly, there are no challenge experiments to demonstrate that a host actively immunized with the claimed compostions would be protected from infection by *H.influenzae* and *M.catarrhalis.* The specification has failed to identify any *M.catarrhalis* antigens other than the 200kDa adhesin protein and has not provided any results with either a *H.influenzae* Hsf protein or heat-shock protein. There are no protocols provided which demonstrate which the

combination of proteins would be effective in multi-valent immunization, nor are there any protocols detailing the amount of protein which is needed to mount a "protective" immune response against *H.influenzae* and *M.catarrhalis* infection, 3) there are no working examples of immunoprotection, absent the immunogenic composition which was patented in the parent Application (the enabled scope), provided in the instant specification, 4) the nature of the invention is a multivalent vaccine which would provide immunoprotection in a mammal against *H.influenzae* and *M.catarrhalis* infection, 5) the relevant skill of those in the art is high yet 6) the state of the prior art has been shown to be highly unpredictable as evidenced by Murphy et al., Yamanaka et al., Ward and Shi et al described in detail above, in generating multi-valent vaccines against *H.influenzae* infection, and otitis media, which would confer protection to a host in need of such a vaccine, and lastly 7) the claims broadly encompass vaccines comprising at least four different antigens, comprising at least one antigen from *H.influenzae* and at least one antigen from *M.catarrhalis*, at least three of which antigens are adhesins and at least one of which adhesins is from *M.catarrhalis*. The claims allow for these antigens to be *any* three adhesin antigens and the one antigen to be any *H.influenzae* or *M.catarrhalis* antigen. The breadth of this scope is not enabled. Therefore, it is maintained that one of skill in the art could not make and/or use the vaccines without undue experimentation.

8. No claims are allowed. The enabled scope was allowed in parent application, 09/353,617. If the claims are amended to this scope, a statutory double patent rejecting will be made. A Double patenting rejection was not made in this Office Action because the instant claims were restricted from the claims allowed in the parent case during

prosecution of the parent application. Accordingly, a Double Patenting rejection would not be proper. However, if the present claims are amended to be indentical, than a statutory double patenting rejection is proper.

9. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

J Graser 2/3/05

Jennifer Graser
Primary Examiner
Art Unit 1645